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TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Medicina II

Proton-Pump Inhibitors Prescription in a Tertiary Teaching Hospital Internal Medicine Ward

José dos Reis Almeida Correia

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Orientado por:

Dra. Teresa Passos da Fonseca

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RESUME

Introduction: Proton-Pump Inhibitors (PPI) are a class of drugs widely used to suppress acid production by the gastrointestinal system. Although in recent years several guidelines on PPI usage have been released, suggesting finite periods of treatment for most cases, there has been a growing rate of the amount of PPI prescription, some with no clear indication. A lack of perception of PPI's side effects may also lead to a global overprescription of this drug class.

Materials and Methods: We conducted a retrospective and descriptive study of the discharge notes of an Internal Medicine ward. The following data was gathered: inpatient identification number, age and sex, admission and discharge information (whether the patient was on PPI and which PPI; whether there was a formal indication for such prescription explicit on the discharge note and which) and data concerning adverse effects.

Results: In a total of 542 patients, 47,2% were on PPI at admission and 55,4% were prescribed PPI at discharge. 48,4% at admission and 49% at discharge were on medication that could cause dyspeptic symptoms; 33,2% at admission and 28,3% at discharge had no explicit diagnose or medication that justified PPI prescription; only 8,6% at admission and 10,7% at discharge had a written diagnosis for such prescription.

Conclusions: These results suggest a great volume of PPI prescription in patients admitted at the studied hospital, increasing at discharge. Except when there is a clear gastrointestinal disease, most discharge notes lack justification for PPI prescription. International guidelines point towards finite PPI treatment periods for most cases, but in no discharge note was such period defined.

Key-Words: Proton-Pump Inhibitors, Overprescription, Guidelines, Prescription adequateness.

The present work expresses the opinion of the author and not that of the Faculty of Medicine of the University of Lisbon.

RESUMO

Introdução: Os Inibidores da Bomba de Protões (IBP) são uma classe de fármacos utilizada para suprimir a produção ácida pelo sistema gastrointestinal. Apesar de recentemente várias recomendações para correta prescrição de IBP terem sido lançadas, estabelecendo para a maioria dos casos períodos finitos de tratamento, verifica-se uma taxa crescente da sua prescrição. A falta de perceção dos efeitos adversos dos IBP poderá também contribuir para este problema.

Materiais e Métodos: Conduzimos um estudo retrospetivo e descritivo das notas de alta de uma enfermaria de medicina interna, recolhendo os seguintes dados dos doentes: identificação, sexo e idade, informação à data de entrada e alta (se medicado com IBP e qual IBP; presença de indicação formal para a sua prescrição e qual), bem como informação sobre efeitos adversos dos IBP.

Resultados: Num total de 542 doentes, 47,2% estava medicado com IBP à entrada e a 55,4% foram-no à data de alta. 48,4% à entrada e 49% à alta estavam medicados com fármacos passíveis de causar dispepsia; 33,2% à entrada e 28,3% à alta não apresentavam diagnóstico ou medicação que justificasse prescrição de IBP; apenas 8,6% à entrada e 10,7% à alta apresentavam um diagnóstico explícito que justifica prescrição de IBP.

Conclusões: Os resultados apontam para um elevado volume de prescrição de IBP em ambulatório, que aumenta à data da alta. Exceto na presença clara de patologia gastrointestinal, à maior parte das notas de alta falta justificação explícita para prescrição de IBP. Apesar da maioria das *Guidelines* internacionais apontar para um período finito de tratamento em grande parte dos casos, em nenhuma nota de alta foi explícito um prazo de tratamento com IBP.

Palavras-Chave: Inibidores de Bomba de Protões, Sobreprescrição, *Guidelines*, Adequação de prescrição.

O presente Trabalho Final exprime a opinião do autor e não da Faculdade de Medicina da Universidade de Lisboa.

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INTRODUCTION

Since their debut in medical practice in 1988 with Omeprazole, Proton Pump Inhibitors (PPI) have revolutionized the treatment and management of gastric-related pathologies and symptoms, proving not only to be well-tolerated but also of superior effect when compared to histamine-2 receptor antagonists (H2RA)[1,2].

The PPI inhibition of gastric secretion is more potent and longer lasting, blocking histamine-2-, gastrin- and cholinergic-mediated sources of acid production and inhibiting gastric secretion at the final common pathway of the H+/K+ adenosine triphosphatase proton pump[3].

In recent years, prescriptions for acid-suppressive therapy, mainly PPI or H2RA, have been growing rapidly, and now this class of therapeutic agents represent one of the highest-cost items in public health care expenditure for drugs[4,5].

PPIs are now among the most common drugs in the world; in the USA, Esomeprazole (Nexium®) was the sixth most prescribed drug by sales in 2013[6]. The Portuguese National Drug Agency (INFARMED) has issued an official document on May the 7th 2017, stating that in 2016 alone 7 Million packages of PPI were sold over the counter in Portugal, accounting for a 30% increase of sales comparing to 2010[7].

Even though several guidelines and recommendations have been presented in order to improve the prescription appropriateness, suggesting for most cases a finite periods of PPI intake (between 4 and 8 weeks of total treatment), dosing and specific situations for such[8-11], an apparent overprescription of these drugs, meaning the lack of apparent or specific indication for such prescription or a prescription made under clear inadequate circumstances, is being documented throughout the years, whether in outpatient departments, hospitalized patients or at discharge[12-22]. This accounts for increased global volume of PPI prescription.

Moreover, not only overprescription of PPI increases the financial burden of National Health Systems[6,23,24], it also is not without health risk: several adverse effects have been documented in patients taking PPI, such a higher rate of *Clostridum difficile* infection (CDI) and healthcare-associated pneumonia (HAP), as well as already

documented relation on magnesium and B12 vitamin reduced absorption and higher rate of bone fractures[25-28].

Considering the above, and since in Portugal there is few information on what concerns PPI prescription by physicians in hospitals, we proposed ourselves to a retrospective, descriptive study. We evaluated the discharge notes of an Internal Medicine ward in a tertiary teaching hospital in Portugal and studied the PPI prescription practices at the time of admission and discharge, bearing in mind the Portuguese government indications for PPI prescription. Our main objectives were to characterize the PPI prescription practices at hospital admission and discharge as well as its adequateness, taking into account the possibility of therapeutic adjustment during hospitalization period, as well as the presence of PPI documented adverse effects.

MATERIALS AND METHODS

After attaining permission from the Internal Medicine Direction from Hospital de Pulido Valente – Centro Hospitalar Lisboa Norte (HPV-CHLN), a tertiary teaching hospital in Lisbon, Portugal, we gathered and evaluated the discharge notes of 4 teams of physicians of an Internal Medicine ward, from January to December 2016. Death certificates, transference notes and readmissions were excluded.

Considering only information explicit on the discharge note, the following data was extracted:

- Inpatient identification number, age and sex;

- Concerning admission and discharge information, we gathered data concerning: whether the patient was on PPI and, if yes, which PPI; whether there was a formal indication for such prescription explicit on the discharge note and, if yes, which;

- Presence of *C. difficile* infection (CDI) or healthcare-associated pneumonia (HAP) during the inpatient period was gathered.

The formal indications considered were based on the only document issued by the Portuguese health governance on PPI prescription (Norma 36/2011, Direção Geral de Saúde[11]), which considers the following as indications for such prescription: Gastro-esophageal Reflux Disease, Esophagitis and Barrett's Esophagus (GERD), Peptic Ulcer (PU), Functional Dyspepsia (DYSP) and Zollinger-Ellison Syndrome (ZE), treatment of *H. pylori* (HP). We named these *DGS-Indications*.

Also, prescribed drugs that may cause dyspeptic symptoms, such as Aspirin, Non-Steroid Anti-inflammatory Drugs (NSAID), Anti-cholinergic drugs, Corticosteroids, Theophylline, Dopaminergic drugs and Bisphosphonates were registered. We named these *DGS-Drugs*.

We also considered the possibility of other reasons for PPI prescription, not explicit in the document, such as oral anticoagulants (Vitamin K Antagonists or Direct Anticoagulants) or pathologies which might precede the indications stated in the document, such as Palliative-care Gastric Cancer. We named these *Extra-DGS*.

After gathering an initial 573 patients, data was filtered so as to exclude incomplete discharge notes (lacking prescription or patient data) and discharge against medical consent. Our final sample was of 542 patients.

We proceeded to a simple retrospective and descriptive evaluation of the database, using Microsoft Excel® tools.

RESULTS

In a sample of 542 patients, we found 58,1% women and 41,9% men, with a mean age of 78,7 years and standard deviation of +/- 12,7 years.

At Hospital Admission

47,2% of patients were on PPI at the admission date, with the following rates regarding the PPI: Omeprazole (55,9%), Pantoprazole (26,2%), Esomeprazole (10,9%), Lanzoprazole (6,6%), Rabeprazole (0%). One patient had simultaneously Omeprazole and Pantoprazole prescribed.

At Hospital Discharge

55,4% of patients were prescribed PPI at discharge, with the following rates regarding the PPI: Omeprazole (60,6%), Pantoprazole (24,7%), Esomeprazole (9%), Lanzoprazole (5,7%), Rabeprazole (0%).

Proton-Pump Inhibitors' Prescription Indication

Bearing in mind the Portuguese health governance indications, considering the patients on PPI, 48,4% at admission and 49% at discharge were on medication that was prone to cause dyspeptic symptoms (DGS-Drugs), although there was not an explicit justification for PPI prescription; 33,2% at admission and 28,3% at discharge had no diagnose or medication written down that justified PPI prescription; 9,8% at admission and 12% at discharge had a justifiable reason for adequate for PPI prescription, even though not stated on the guideline (Extra-DGS); only 8,6% at admission and 10,7% at discharge had a written diagnosis for such prescription in accordance with the stated document indications (DGS-Indications).

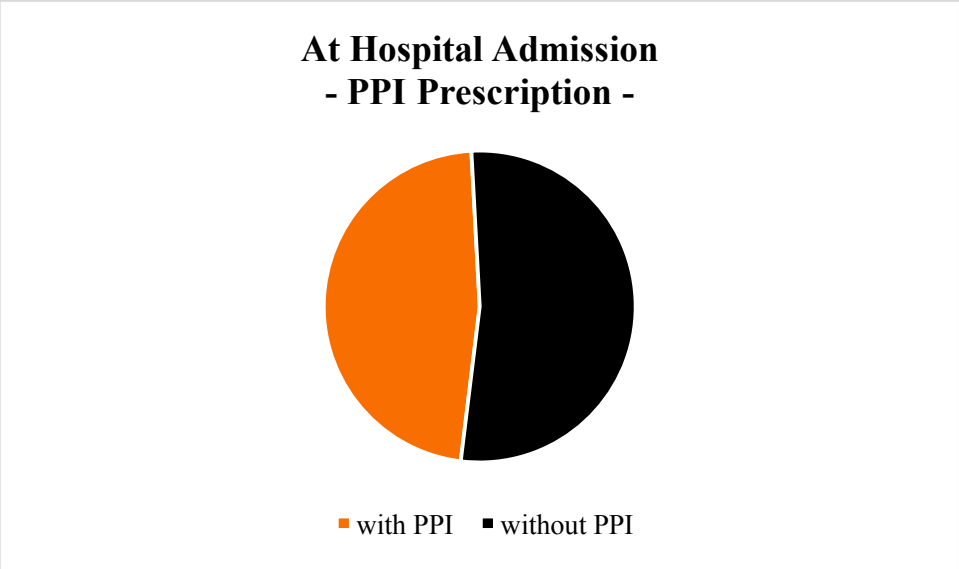

Chart 1 - Rate of PPI prescription at admission

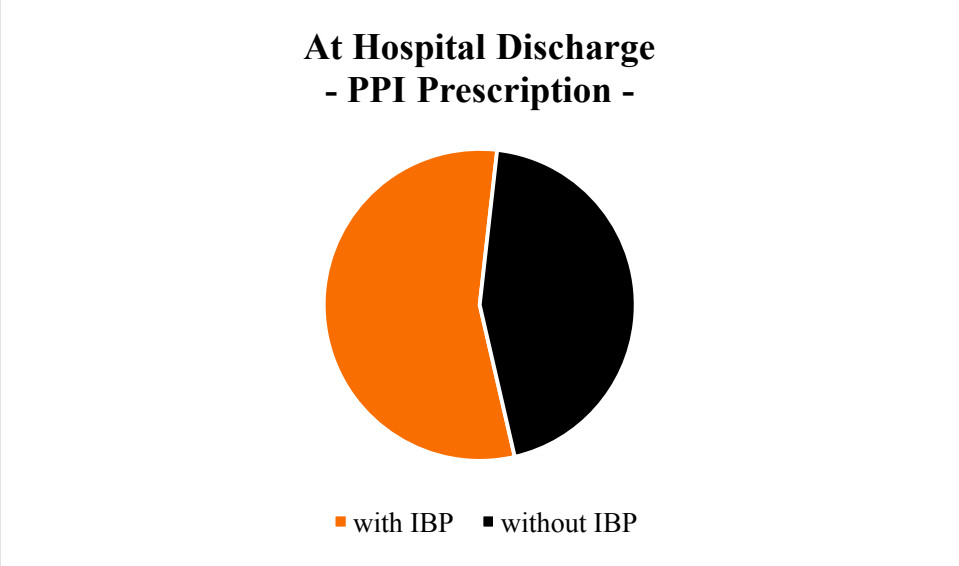

Chart 2 - PPI prescription at hospital discharge

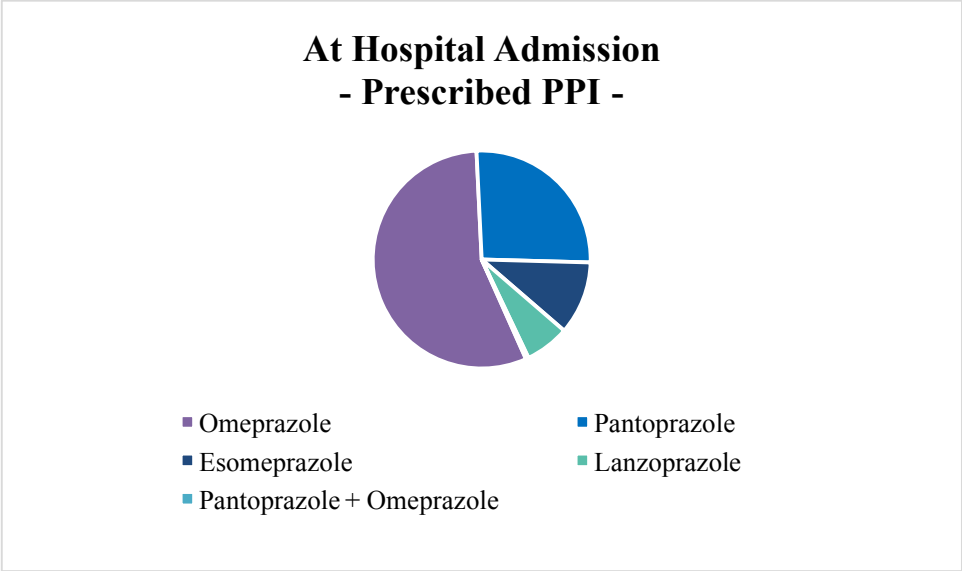

Chart 1 – Prescribed PPI differences at admission

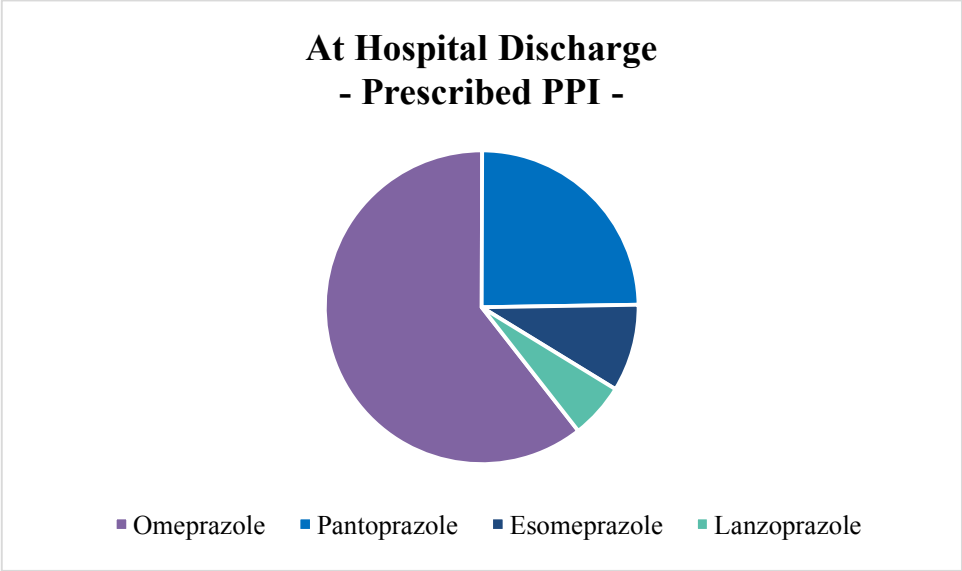

Chart 2 – Prescribed PPI differences at hospital discharge

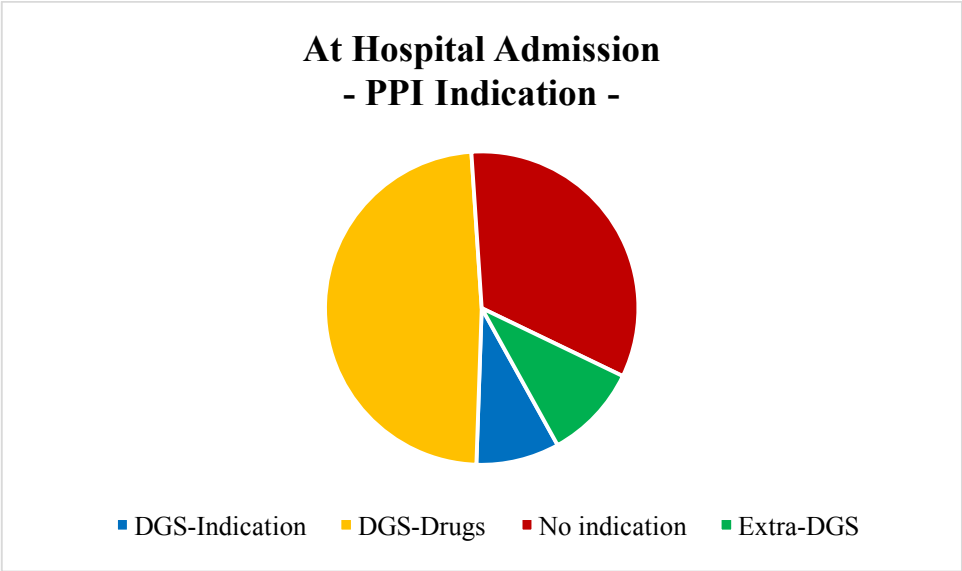

Chart 3 - PPI prescription indication at admission, in patients on PPI

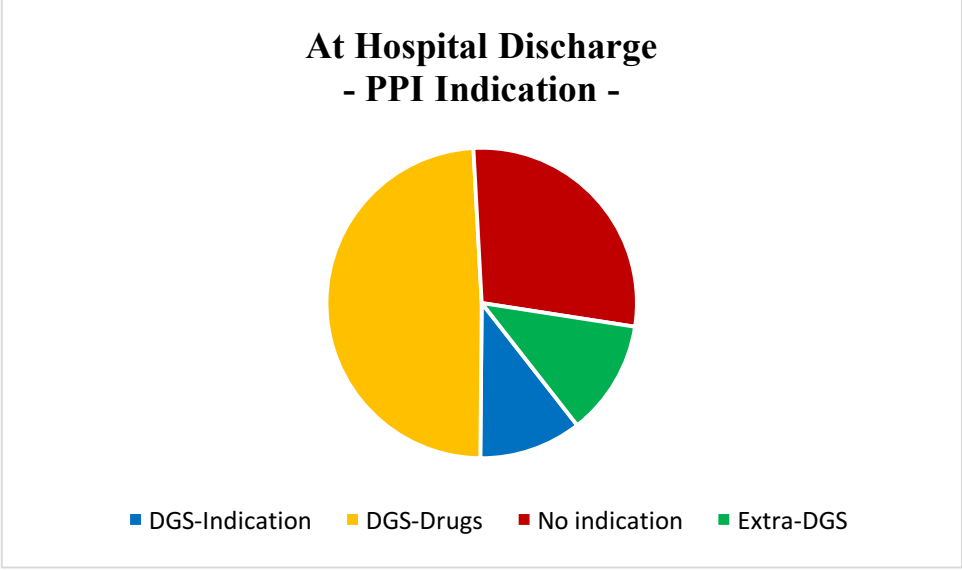

Chart 4 - PPI prescription indication at hospital discharge, in patients on PPI

Global Overview

Globally, 41,9% of patients were admitted and discharge with no PPI prescription; 44,5 of patients were admitted on PPI and discharged with a PPI prescription; 2,7% of the sample was admitted with PPI prescription and discharged without it; 10,9% of the sample was admitted without PPI prescription and discharged with a PPI prescription.

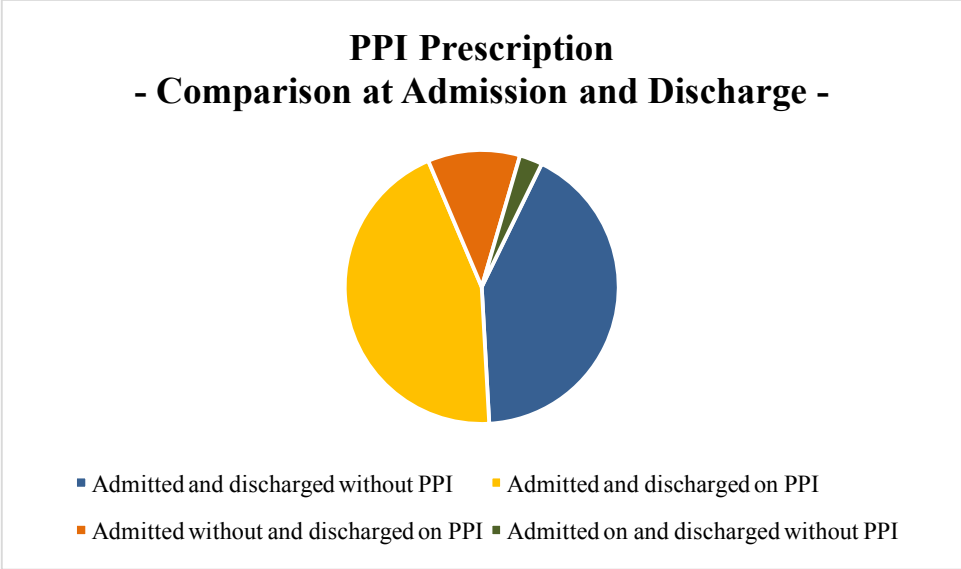

Chart 5 - Comparison between PPI prescription practice at admission and discharge

When prescribed at discharge, there was never a defined period for PPI treatment defined on the discharge note, e.g. 4 weeks. In a few, there was indication for a posterior prescription adjustment, to be considered by the assistant doctor.

Also, we found a total of 0,3% that had *C. difficile* infection and 2,2% that had healthcare-associated pneumonia during the hospitalization period.

DISCUSSION

At first glance, our results point in the direction of a large volume of PPI prescription, with 47,2% of patients admitted on and 55,4% discharged on PPI: an increase of 8,2%.

Our findings are compatible with other studied populations, where the PPI prescription volume at admission or discharge varied between 32% and 85% [14,22].

Omeprazole was the most prescribed PPI in our sample (55,9% at admission and 60,6% at discharge), which contrasts with other realities, where Pantoprazole or Esomeprazole are widely prescribed [5,6]. It would be interesting to better understand the reasons for such reality, since Omeprazole was the first PPI released and has more described pharmacological interaction, for example, with Clopidogrel, than more recent PPI.

The evaluated sample had a mean age of 78,7 years. This can influence the prescription practices due to polymedication with other drugs, such as NSAIDs, Calcium-Channel Blockers or Aspirin, which may cause dyspeptic symptoms. This may in part justify the rate of PPI prescription at admission and discharge, on patients that were on medication which could cause dyspeptic symptoms: 48,4% and 49%, respectively (DGS-Drugs). In these cases, there was not a documented reason for such concomitant prescription. We cannot thus assure that the results mirror the physicians' true clinical reasoning, because in most cases what lacked was an explicit, written down diagnose or justification in the discharge note, for a PPI prescription. Our results point towards a strong link between possibly dyspeptic medication or polymedication and concomitant PPI prescription.

A strong relation between PPI prescription and gastric-related pathologies would be expected. However, considering the portuguese healthcare governance document, among the PPI prescribed patients, only 8,6% of patients at admission and 10,3% at discharge had an explicit indication that justified it (DGS-Indications). Almost one third of patients at admission (33,2%) and at discharge (28,3%) had no explicit diagnose or medication prone to suggest PPI prescription, according to the stated document and our team discernment. This information points clearly towards the overprescription of PPI in the studied sample.

Considering Hwang et al.'s study[29], where the variability in the rate of inappropriate use of acid suppressive therapy was found to vary depending on which guidelines were applied to the same database. It is hard to find a global concept for appropriateness for PPI prescription, thus being our findings true to the considered Portuguese governance indications.

Thus, although we cannot conclude for sure that there is an overall lack of adequate prescription, we can surely affirm that physicians rarely explicit the reason for PPI prescription and its period of intake on discharge notes. This can become a chronic issue: when there is a readmission at a hospital facility, neither the patient or the attending physician may be aware of the reason for PPI prescription or the length of treatment, thus continuing a vicious cycle of unjustified PPI prescription.

Moreover, in no discharge note was a therapeutic period for PPI defined, which leads us to believe the patient will continue on PPI at least until further evaluation. This was already studied previously, resulting in unnecessary increased drug cost and adverse effects[21].

We believe that this lack of justification may reside on physicians' misperceptions on PPI safety, an idea supported by the recent launched campaign by INFARMED[7], alerting to the increased expense due to PPI prescription and to the pathologies and periods of treatment already studied and established for this drug-class. This continuous prescription can sometimes happen without further questioning the patients or the attending physician about the reasons for PPI intake. The trust of physicians into each other's clinical reasoning and prescription adequateness may be a reason for this lack of questioning and further overprescription of PPI. Also, medical students' education may have a life-impact on what concerns prescription practices, since students can be taught a not-always-valid gastric protection effect of PPI, for example, when the patients is under polimedication. It may be of value to demystify the gastric-protection reality of the PPI class, since it is not without risk, and to further address its side effects and adequateness of prescription.

Concerning recently published works, we strongly believe that application of PPI prescription guidelines in hospitals may improve the quality of prescription and reduce the expense on such drugs[13,21].

Moreover, education and intervention on medical staff, proves efficient in addressing inappropriate PPI prescription[21]. In a 2006 study by Liberman et al.[30], a fall in inappropriate Stress Ulcer Prophylaxis with PPI was confirmed after a practice-based educational intervention, from 59% to 33% after a 6-month follow-up, with the inappropriate prescription at discharge falling from 25% to 7%. Thus, and bearing in mind the recent INFARMED campaign, we suggest that education on PPI prescription among physicians in Internal Medicine wards should greatly reduce the overprescrition of these drug-class. This could be easily performed once a year, considering that the new Internal Medical Residents should be since an early start of their clinician career bear in mind the appropriateness of PPI prescription, so as to teach it along.

Physicians sensibilization for a better and more correct PPI prescription may help admitted patients to leave the hospital with a drug prescription with a tailored approach, cutting down on superfluous medication that is rarely without risk.

Although a strong connection between CDI or HAP with PPI prescription there could not be established in our study, since we did not consider the whole hospitalization period, there is already evidence on these pathologies as an adverse effect of PPI intake[22,27-29].

Our study's limitations reside within the retrospective character of it, which prevented us from interviewing the physicians and patients at the moment of admission and discharge. This could have allowed us to understand whether there was a defined diagnose for PPI prescription and the reason for the PPI chosen: as stated above, pharmacological interactions may vary between Omeprazole and the remainder of PPI. We weren't able to gather data on whether or not the patients were on PPI during the hospitalization period, which could further improve our discussion.

Due to time limitation, we were only able to study four Internal Medicine teams. With the study of the prescription practices of all Internal Medicine teams, we could develop a wider database, concerning the entire teaching hospital.

Also, the wide variety of clinical guidelines on PPI prescription and the lack of an international accepted document, although enriching the discussion of such a subject, may on the other hand difficult the creation of a global consensus on what concerns PPI: a consensus that could have a massive impact on the PPI-producing agencies.

CONCLUSIONS

It is clear that there is a great volume of prescription of PPI in patients admitted at our tertiary teaching hospital, which increases at discharge.

Except when there is a clear gastrointestinal disease, most discharge notes, account for almost a third of the sample, lack explicit justification for PPI prescription. This points towards a overprescription of PPI and lets one wonder whether the physicians feel the need to justify a PPI prescription.

Even though most international guidelines are clear about a 4 to 8-week treatment period in most cases, in no discharge note was a period of treatment with PPI written down.

Education initiatives with healthcare providers and hospital internal guidelines may contribute to a more adequate PPI prescription practice, and to ease its burden on patients' health, patients' expense with over-the-counter medication and on health systems' global expenses.

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